Comments on
Benchmark Dose Estimates Presented in the
NTP-CERHR Expert Panel Report on the
Reproductive and Developmental Toxicity of Acrylamide

Submitted to
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In the report entitled, "*Draft NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Acrylamide*," benchmark dose (BMD) values were derived for approximately a dozen data sets for the developmental and reproductive effects of acrylamide in laboratory rodents. However, the purpose for deriving BMD values in the report was unclear, since no rationale was provided and since BMDs were not developed in similar reports prepared by NTP-CERHR (*viz.*, report for 2-bromopropane, dated March, 2002 does not present benchmark doses).

Certainly BMD values in the subject draft report are not needed to meet the goals of the CERHR report, and, therefore, they should be excluded. That notwithstanding, if the BMD values were to be retained in the final report, two possible advantages could be achieved from

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their inclusion, and they are described below, along with specific comments on the implementation of BMD methods in the report.

First, a potential reason for deriving benchmark doses, not articulated in the CERHR draft, would be to determine whether or not existing noncancer risk assessments (such as a Reference Dose or RfD) for acrylamide are also protective against risks of reproductive and developmental impairment. Currently, noncancer risk assessment for acrylamide is based on its neurotoxicity in rats following subchronic exposure via drinking water (Burek *et al.*, 1980), with the realization that acrylamide at sufficient doses has also been shown to cause neurotoxicity in humans. An oral **reference dose of 0.0002 mg/kg-day** protective of neurotoxicity in humans has been derived from LOAEL and NOAEL values of 1 and 0.2 mg/kg-day, respectively, obtained from laboratory animal studies (IRIS,2004).

Benchmark doses presented in the draft CERHR report based on reproductive and developmental toxicity generally ranged from 5 to 44 mg/kg-day, with the corresponding lower confidence limits ranging from 2 to 36 mg/kg-day. After careful examination, we have found that benchmark dose estimates for the neurological effects of acrylamide (Burek *et al.*, 1980; Johnson *et al.*, 1986; Friedman *et al.*, 1995) range from 0.4 to 3.4 mg/kg-day, with the corresponding lower confidence limits ranging from 0.2-0.9 mg/kg-day. Because the BMD values are all considerably higher than the NOAEL and BMD values for neurological effects, we conclude that the existing RfD for acrylamide is protective of the risks of reproductive and developmental toxicity.

Second, another potential reason for deriving BMD values, also not articulated in the CERHR draft, would be to improve comparisons made across the reproductive and developmental studies that would otherwise be made using NOAEL and LOAEL values, which are inherently imprecise. However, limitations in the BMD values as derived in this draft report limit their usefulness for comparison purposes. Those limitations include:

- A challenging aspect of using reproductive and developmental toxicity in dose-response assessment is the potential for interdependency due to litter effects. In the draft report, no consideration or discussion is given for potential litter effects in the BMD values presented. The BMD values were all derived using models for continuous data (*e.g.*, linear, power) which ignore the potential for litter effects. USEPA's BMD program (Version 1.3.2) has dose-response models capable of addressing these effects; they include the "nlogistic," "NCTR," and "Rai & Van Ryzin" models. However, these models are more data intensive than the simpler models adopted in CERHR's draft. Because of the additional effort required by the nested models that can address litter effects, we recommend identifying the most robust reproductive study and

developmental study to model dose-response relationships, rather than deriving BMD values from all possible studies, which is not informative to the users of the information.

- Remarkably in the CERHR draft report, very little detail is presented on the dose-response modeling efforts. At a minimum, the outputs of the BMD program should be included as an appendix to the report, which represents current state-of-the-art for such estimates in scientific reports.

- Lastly, one particular data set resulted in very small BMD values in CERHR's draft report. Specifically, in Figure 8 (second panel) and in Table 29 of the draft report, BMD values for post-implantation loss/litter were described as being "<<1" mg/kg-day. The low value obtained for this data set, which if correct would suggest that acrylamide would be a potent reproductive and developmental toxicant, is the result of improper dose-response modeling methods, and hence is incorrect. At least two ways exist to correctly perform the dose-response modeling for this data set:

    - (a) Because the data are expressed as a percentage, the Benchmark Response (BMR) type should be specified as absolute deviance ("abs. dev.") rather than as relative deviance ("rel. dev."); or

    - (b) Transform the data to % post-implantation success/litter by subtracting each of the % loss values from 100%.

    In either case, the BMD value for this data set should be in the range of 10 to 15 mg/kg-day (based upon visual inspection of Figure 8) rather than "<<1" mg/kg-day as indicated in the draft report.

If these issues are not, or cannot be, addressed in a revised version of the draft report, then comparisons across studies are better made using the NOAEL and LOAEL values, despite their inherent imprecision.

References

BMDS. Benchmark Dose Software, Version 1.3.2. Downloaded from USEPA website: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20167

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